425 A Small Molecule Glycomimetic Antagonist of E-selectin and CXCR4 (GMI-1359) Prevents Pancreatic Tumor Metastasis and Offers Improved Chemotherapy

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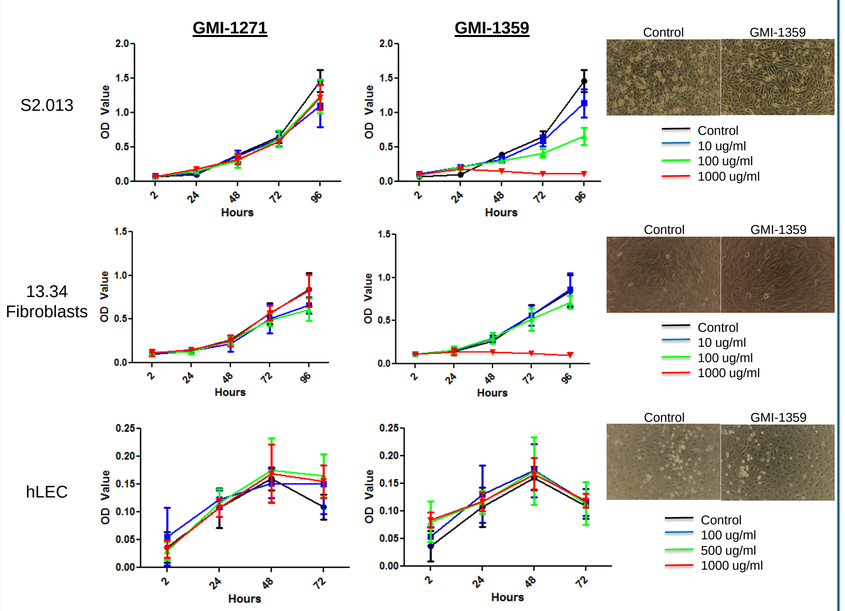
ABSTRACT

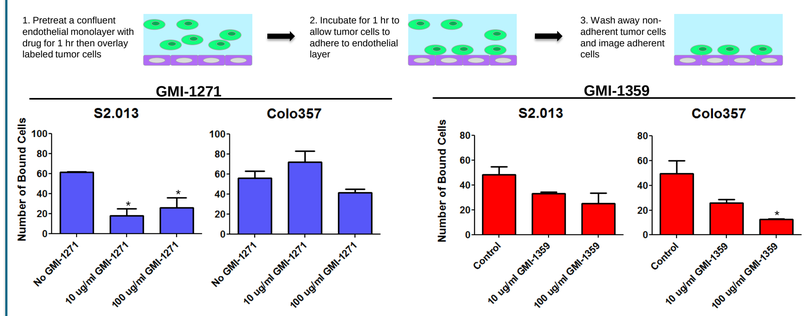
The tumor microenvironment's cellular and molecular composition includes a complex matrix that encases tumor cells and presents a conundrum in respect to pancreatic tumor therapy. On one hand, the dense desmoplastic reaction that accompanies growth of well differentiated pancreatic tumors reduces blood flow to tumors and creates an environment in which it is difficult to deliver therapies. On the other hand, elimination of certain stromal elements enhances the aggressiveness and metastatic potential of pancreatic cancer cells. Several current studies are attempting to target stroma in an effort to enhance delivery and efficacy of therapeutic agents and to block metastasis. We have investigated the activity of GMI-1359, a potent dual antagonist that targets both E-selectin and CXCR4. Adhesion protein E-selectin plays an important role in the tumor microenvironment by regulating cell contacts, including tumor cell binding to vascular and lymphatic endothelial cells during extravasation. Chemokine receptor CXCR4's role in the chemoattraction of tumor cells toward endothelial cells (ECs) contributes to tumor microenvironment remodeling by influencing lymphangiogenesis/angiogenesis, tumor cell survival/proliferation, and tumor stem cell mobilization. Our *in vitro* studies show that pancreatic ductal adenocarcinoma (PDAC) cells do not attract growth of lymphatic nor vascular ECs toward themselves. However, tumor associated fibroblasts, a major component of the PDAC tumor microenvironment, significantly increase EC directional migration. GMI-1359 completely blocked lymphatic and vascular EC migration toward fibroblast cells and disrupted these cell-cell interactions. In addition, GMI-1359 inhibited the capacity of invasive PDAC cell lines S2.013 and Colo357 to bind and migrate across EC barriers. The dual antagonist was more effective than an independent small molecule E-selectin inhibitor. We evaluated the capacity of GMI-1359 to inhibit growth and metastasis of orthotopically implanted S2.013 cells with and without administration of Gemcitabine. Two weeks post implantation, mice were treated by intraperitoneal injection for 4 weeks with either PBS once daily; 40 mg/kg GMI-1359 once daily; 100 mg/kg Gemcitabine every 4 days; or a combination of GMI-1359 and Gemcitabine. GMI-1359 treatment slightly, but not significantly, decreased primary tumor size as compared to the vehicle control. However, GMI-1359 in combination with Gemcitabine significantly reduced metastasis of this tumor to liver and diaphragm as compared to mice that received only Gemcitabine. Further studies of GMI-1359 are warranted to understand its potential for disrupting cellular contacts and blocking pancreatic tumor dissemination through the vascular and lymphatic systems, and for enhancing the efficacy of chemotherapeutic approaches to pancreatic cancer.

GMI-1359 Inhibits PDAC and Fibroblast Proliferation



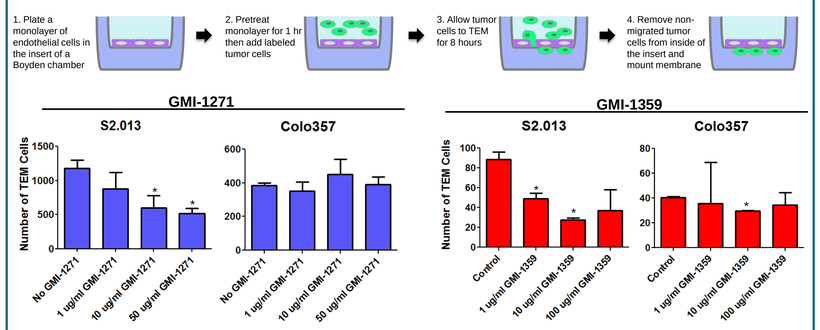
Also performed with Colo357 and HUVECs with similar results

GMI-1359 Inhibits PDAC Binding to Lymphatic Endothelium



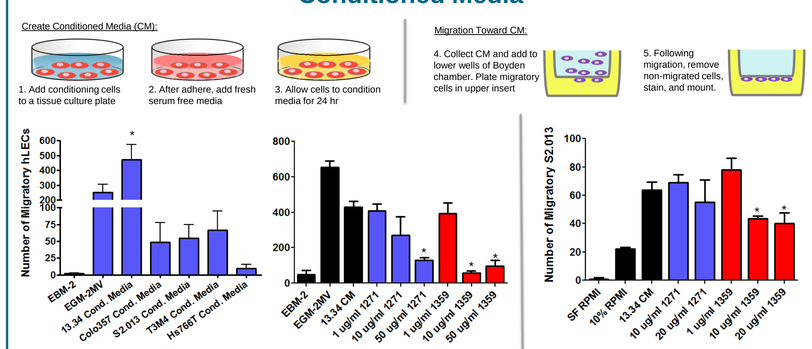
Also performed with a HUVEC monolayer with similar results

GMI-1359 Inhibits PDAC Transendothelial Migration



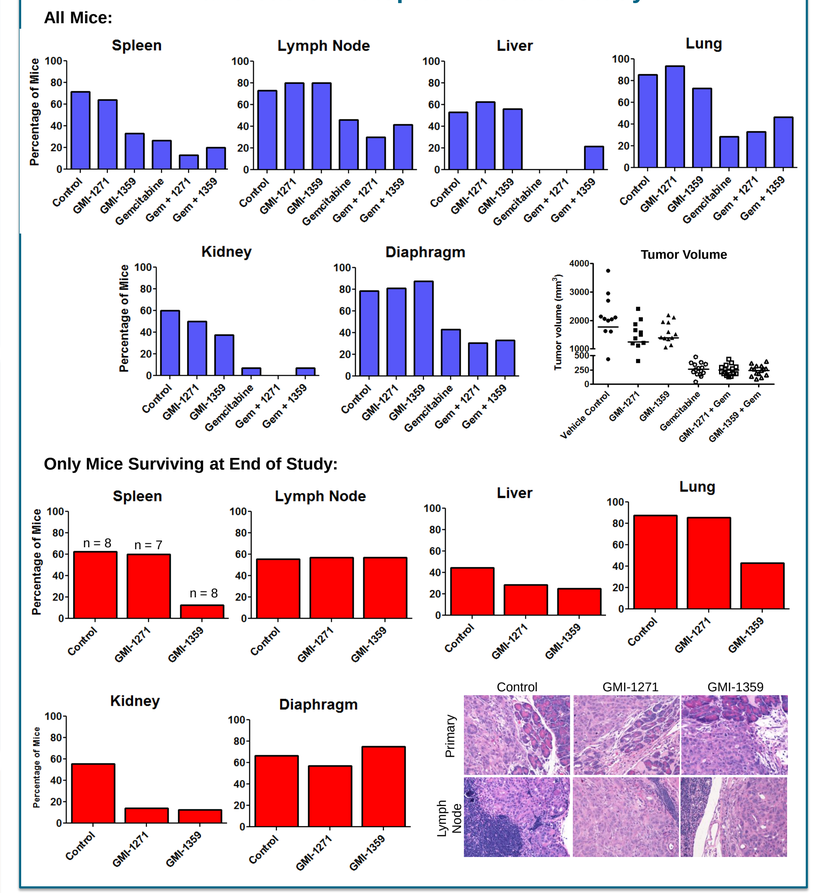
Also performed with a HUVEC monolayer with similar results

GMI-1359 Inhibits Endothelial Migration Toward Fibroblast Conditioned Media



Also performed with a HUVEC monolayer with similar results

Pancreas Orthotopic Metastasis Study



Conclusions

- High dose GMI-1359, but not GMI-1271, inhibits PDAC cell and fibroblast proliferation in a dose dependent manner. High dose GMI-1359 has no effect on endothelial cell proliferation.
- GMI-1359 decreases the binding of PDAC cells to a lymphatic endothelium and also reduces these cells' ability to undergo transendothelial migration in a dose dependent manner.
- GMI-1359 (and high dose GMI-1271) inhibits hLEC migration toward fibroblast conditioned media. GMI-1359 also inhibits PDAC cell migration toward fibroblast conditioned media.
- When used alone, GMI-1359 inhibits metastasis in a pancreas orthotopic tumor model. High dose Gemcitabine also decreases metastasis. When used in combination with Gemcitabine, GMI-1271 further inhibits metastasis while GMI-1359 has no increased benefit.

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